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Intravenous Lacosamide in refractory nonconvulsive status epilepticus

L. Mnatsakanyan [a,b,*], J.M. Chung [a,c], E.I. Tsimerinov [a,c], D.S. Eliashiv [a,d]

[a] Department of Neurology, Cedars-Sinai Medical Center, Los Angeles, CA, United States
[b] Department of Neurology, University of California, Irvine, CA, United States
[c] Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, United States
[d] Department of Neurology, David Geffen School of Medicine at UCLA, Los Angeles, CA, United States

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ABSTRACT

Background: Many patients present with refractory Status epilepticus (SE) despite multiple anti-epileptic drugs (AEDs). Lacosamide (LCM) was recently approved as an adjunct AED for partial-onset seizures. It has unique mechanism of modulating voltage-gated sodium channels by enhancing their slow inactivation. LCM has demonstrated efficacy in animal models of pharmacoresistant seizures. To date, there are isolated anecdotal reports of LCM use in SE.
Objective: To report a single center experience with IV Lacosamide in patients with NCSE.
Methods: Pharmacy records were reviewed to identify patients with SE who received IV LCM in our institution. Data on demographics, response to therapy and adverse effects/outcomes were analyzed. All patients had continuous EEG monitoring.
Results: 10 patients (4 men, 6 women), age 16–90 years with refractory SE were given LCM. Eight patients were in focal non-convulsive SE (NCSE), 2 were in generalized non-convulsive SE. The etiologies included anoxic brain injury, idiopathic, encephalitis, tumor, posterior reversible encephalopathy syndrome (PRES), stroke, and AVM. IV LCM was added after traditional AEDs, including drug-induced coma in some, failed to control the SE. NCSE resolved in 7/10 patients whereas 1/10 patient showed partial response with cessation of NCSE but still frequent electrographic seizures and 2/10 patients were resistant to therapy.
Conclusions: LCM is a useful adjunct in refractory NCSE. The IV formulation allows prompt administration in the intensive care unit setting. Response was seen especially in focal SE. Similar to other AEDs, response was poor in patients with postanoxic injury. Our data is limited by the small number of patients. Larger controlled studies are necessary to assess accurately the efficacy of IV LCM as an early treatment of SE.

1. Introduction

Status epilepticus (SE) is associated with significant morbidity and mortality. SE is encountered frequently in critical care setting and is often refractory to treatment. The established paradigm in most centers for SE treatment utilizes first generation AEDs.[1–3] Nonconvulsive status epilepticus (NCSE) is a commonly under-recognized condition in critically ill patients.[4] In neurological ICU, the prevalence of NCSE may be as high as 10.5%.[5] The prevalence of non-convulsive seizures (not NCSE) may be even higher, reaching 18% on continuous EEG monitoring.[6] Up to 20% of patients with SE after initial treatment can evolve to become NCSE.[7]

Lacosamide (LCM) is a novel anticonvulsant approved in 2008 by the Food and Drug Administration as an adjunctive therapy for partial onset seizures in patients with epilepsy aged 17 and older (United States).[8,9] LCM modulates voltage-gated sodium channels by enhancing slow inactivation without affecting the fast inactivation,[10,11] which is expected to normalize activation thresholds, thus decreasing pathophysiological neuronal hyper-excitability. LCM has minimal (<15%) protein binding and drug–drug interactions.[13] Intravenous (IV) formulation is easy to handle, has the same safety profile as oral formulation.[10] The maximum drug concentration is reached at the end of infusion. To characterize the effectiveness and role of LCM in SE, mainly in ICU settings, we retrospectively analyzed the outcome of patients in SE treated with IV LCM in addition to traditional AEDs.

2. Methods

Consecutive patients who were diagnosed with NCSE at Cedars Sinai Medical Center, Los Angeles, California between August 2009

* Corresponding author at: 8730 Alden Dr #E-204, Los Angeles, CA 90048, United States. Tel.: +1 310 423 6472; fax: +1 310 423 0148.
E-mail addresses: mnatsakl@uci.edu (L. Mnatsakanyan), Jeffrey.Chung@cshs.org (J.M. Chung), Evgeny.Tsimerinov@cshs.org (E.I. Tsimerinov), Dawn.Eliashiv@cshs.org (D.S. Eliashiv).

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and August 2010 were reviewed. There are no current universally accepted definitions of NCSE. There are no pathognomonic clinical signs or EEG features that are specific for NCSE. NCSE can be defined as a prolonged state of impaired consciousness or altered sensorium associated with continuous paroxysmal activity or electrographic discharges on the EEG.[4] Pharmacy records were examined to identify patients who received IV LCM during the course of their treatment. All patients with the diagnosis of NCSE were monitored with continuous EEG monitoring. Data including demographics, etiology, seizure semiology, concomitant AEDs and outcome was collected utilizing our IRB approved data collection tool.

3. Results

We identified 10 patients (4 men and 6 women), ages between 16 and 90 years, with nonconvulsive status epilepticus, treated with IV Lacosamide. Eight patients had initial clinical presentation with manual automatisms, focal motor twitching and impaired consciousness or generalized tonic–clonic activity followed by persistent focal subclinical, electrographic seizures despite aggressive management, and two patients were in generalized electrographic status. The etiologies included anoxic brain injury due to asystole, herpes simplex virus (HSV) encephalitis, idiopathic, glioma, brain metastases, posterior reversible encephalopathy syndrome (PRES), arteriovenous malformation (AVM) and stroke (Table 1). SE was the initial presentation in 6/10 patients. Only four patients had previous history of complex partial seizures secondary to a structural lesion.

IV LCM was administered to the patients after standard treatment for SE failed to control the seizures within the 1st or 2nd day of adequate therapy. The median loading dose of IV LCM was 200–300 mg infused within 30 min per pharmacy protocol. Current approved IV loading dose of LCM is up to 200 mg; however 300 mg doses have been used safely as well. The maintenance dosage ranged from 100 to 200 mg every 12 h. Concomitant AEDs used prior to the addition of LCM included phenytoin (PHT), levetiracetam (LEV), valproic acid (VPA), midazolam, propofol and pentobarbital induced coma. In addition, some of these patients were given topiramate (TPM) and lamotrigine (LTG) via NG tube. All the patients received IV lorazepam upon initial presentation. LCM was the last anti-convulsant added to the regimen preceding termination of NCSE, only patient #1 had TPM added a few hours apart from LCM. Serum levels of all AEDs were maintained therapeutic. The AEDs were added in sequence of treating physicians' preference. The first line therapy was according to current guidelines. The maintenance dose of PHT ranged from 300 to 400 mg/day, LEV 3000–4000/day, TPM 300–400/day, clonazepam 2–4 mg/day, phenobarbital 120–180 mg/day. The continuous anaesthetics were titrated to the desired level of anaesthesia and EEG response based on hemodynamic and side effect tolerability.

SE resolved in 7/10 patients. Although only one patient (patient #3, Table 1) demonstrated an immediate termination of SE after the LCM administration, the other patients eventually had resolution of SE. We do not have more precise timing between adding the LCM and termination of NCSE in all patients due to retrospective nature of this study. All seven patients eventually recovered close to their pre-admission baseline state with a seizure free outcome (follow-up range 1 week–10 months). Oral LCM as an adjunct AED was maintained in most of these patients (Table 1). Patient #9 (Table 1) had advanced lung cancer with widespread brain metastases, resulting in cerebral edema. She continued to have periodic lateralized epileptiform discharges (PLEDs) on EEG, but less persistent, and fewer brief electrographic seizures, and was eventually given comfort care per the family's wishes. Two patients with post-anoxic brain injury and refractory non-convulsive generalized SE did not respond to treatment, and they had their care withdrawn. Patient #10 (Table 1) had advanced breast cancer without brain metastases showed complete resolution of electrographic seizures and PLEDs on EEG and remarkable improvement of neurological status; however, she later suffered multiple non-neurological complications and was given comfort care as well. No patient in our study population had a documented early or delayed adverse side effect including a hemodynamic instability during the infusion, injection site reactions, rash, change in other AED serum levels or electrolytes in a close relationship to LCM introduction or significant drug–drug interactions. On post discharge follow up ranging 3 weeks to 10 month depending on discharge date in relation to the study period, none of the patients had records of readmission for seizures and some remained seizure free on and off AEDs on follow up clinic visit.

4. Discussion

We reviewed our initial clinical experience with intravenous LCM in patients with focal partial and generalized NCSE in our medical center with a large neurological intensive care unit (ICU) and about 400 continuous EEG monitoring studies per year. To date there are no universally accepted definitions of NCSE.[4] There are no pathognomonic clinical signs or EEG features that are specific for NCSE. NCSE can be defined as a prolonged state of impaired consciousness or altered sensorium associated with continuous paroxysmal activity or electrographic discharges on the EEG.[4] Our definition of NCSE was similar, continuous evolving electrographic rhythmic patterns in patients without obvious clinical behavior such as motor twitching, jerking, head and gaze deviation, automatisms, but with persistent confusional state, obtundation and coma without return to baseline level of mentation and interaction. The patients with periodic non-sustained and non-evolving EEG patterns were not included. Some of the initial behavior included manual automatisms and limb stiffening (Patient #1), focal facial and arm twitching (patients #3, 5 and 7) with impaired consciousness, generalized tonic–clonic activity (patients #4 and 10) without recovery to baseline state followed by subclinical persistent electrographic activity without improvement of cognition. Lacosamide is not FDA approved for treatment of status epilepticus; however multiple randomized pre-clinical and clinical studies have shown LCM as an effective adjunct antiepileptic medication.[9,16–18] However, there is limited data consisting of mostly single case reports on the efficacy of LCM in controlling SE. Tilz et al. reported cessation of convulsive SE with a single dose of LCM after lorazepam, levetiracetam (LVT) and midazolam failed to control the seizures.[14] Turpín-Fenoll et al. reported a 72-year-old male with an ischemic lesion and partial SE successfully treated with LCM,[12] and another patient with post anoxic, late-onset myoclonus that responded well to LCM.[15]

Lacosamide has shown effectiveness in a number of animal models, such as maximal electroshock (MES) test induced seizures in rats and mice by preventing the seizure spread. In a pentylenetetrazol paradigm, LCM was shown to lack a pro-convulsant or seizure-threshold lowering activity. Interestingly, LCM displayed a higher potency in the 6-Hz model of psychomotor seizures—a model for treatment resistant seizures[19] compared to that of newer generation AEDs, thus suggesting a potential role in pharmacoresistant seizures.[20] In the homocysteine model of self-sustaining status epilepticus (SSSE), LCM appeared less potent against generalized tonic clonic seizures (GTCS); however, its efficacy was potentiated by low dose diazepam.[19] Furthermore, LCM reduces the cumulative SSSE duration and neuronal hippocampal damage following perforant path stimulation, and prevents spontaneous GTCS in the cobalt/homocysteine model of SSSE based on previous works.[21] In fact, there are preliminary

Table 1
Patient characteristics, EEG findings, concomitant AEDs, outcome.

Patient	Age/sex	Diagnosis	EEG localization of ictal patterns	Other AEDs	Outcome	Previous seizures	Discharge AEDs
1	70 M	Unknown	Left temporo-occipital region	PHT, LEV, MDZ, PB, TPM, PTB Clonazepam	Recovered No seizures	None	LCM LEV TPM
2	90 F	Asystole	Persistent generalized spike wave complexes	LEV, VPA, Propofol, MDZ	Withdrawal of care	None	
3	33 M	Glioma Resection	Left fronto-temporal	PHT, LEV	Recovered No seizures	Yes	LCM LEV
4	81 F	HSV encephalitis	Left hemispheric	PHT, LEV	Recovered No seizures	None	PHT, LCM, LEV
5	16 F	Frontal AVM Resection	Anterior quadrant	LEV (allergy to other AEDs)	Recovered No seizures	Yes	LCM LEV
6	61 M	Asystole	GPED	PHT, LEV	Withdrawal of care	None	
7	61 M	Multifocal glioma	Left hemispheric seizures and frontotemporal PLED	LEV PHT VPA	Recovered/some seizures	Yes	LCM LEV
8	46 F	Left hemispheric chronic infarct	Left posterior quadrant	PHT LEV VPA	Recovered	Yes	VPA LEV LCM
9	60 F	Multifocal brain metastases	Left posterior quadrant	PHT MDZ PTB	Comfort care/EEG: PLEDs, fewer seizures	None	
10	55 F	PRES/advanced breast CA without brain metastasis	Occipital region	PHT MDZ LEV	Resolution of seizures. Later, comfort care	None	

Abbreviations: AED: antiepileptic drugs; AVM: arteriovenous malformation; GPED: generalized periodic epileptiform discharges; HSV: herpes simplex virus; LCM: Lacosamide; LEV: levetiracetam; PHT: phenytoin; PTB: pentobarbital; PRES: posterior reversible encephalopathy syndrome; TPM: topiramate; MDZ: midazolam; VPA: valproic acid.

reports of IV LCM being useful as a first-line therapy in patients in SE when other agents are felt to be unsuitable.[25,26]

All, but one of our patients with focal partial NCSE (7/8), showed resolution of the ictal electrographic discharges. Subsequently, six patients improved and remained seizure free upon discharge. 6/6 patients were discharged on a combination of LCM and LEV. In addition PHT was the third AED on discharge in 2 patients, TPM in one and VPA in one (Table 1). One patient (1/8) with multiple brain metastases did show a partial response as her EEG demonstrated persistent PLEDs but fewer and shorter electrographic seizures.

Two other patients who suffered cardiopulmonary arrest and resultant anoxic brain injury showed no response to multiple anticonvulsant therapy including Lacosamide and remained in generalized NCSE. However, it should be noted these patients also had significant co-morbidities due to multiorgan failure. Our retrospective review was also notable for 9/10 subjects already receiving levetiracetam prior to adding the Lacosamide yet still requiring additional AEDs, which questions the efficacy of levetiracetam in acute settings as well.

In summary, our study data suggests that IV LCM can be efficacious and safe in managing patients with refractory NCSE as an adjunctive agent. Although refractory SE is known to be more resistant to treatment,[23,24] 7/10 patients in our study demonstrated a response with the cessation of SE after the addition of LCM. There was, however, no demonstrated efficacy in treating generalized NCSE associated with post-anoxic injury, which is known to be highly resistant to anti-epileptic medications[22,27] and may represent separate subset. No adverse side effects or drug–drug interactions were seen in these acutely ill patients. The availability of IV formulation provides the benefit of easier administration and rapid action when oral intake is contra-indicated. LCM is renally excreted; and the dosage should be adjusted in patients with renal failure. We cannot comment as to the efficacy of LCM as initial treatment of SE since all our patients had LCM administered as adjunct therapy. There is currently no evidence supporting the use of LCM as an initial agent for SE. We can not exclude a possibility of selection bias affecting our results given the study period of one year and our tertiary care center having a high number of neurosurgical patients with acute CNS insults that might not represent the typical population presenting with status epilepticus. In other centers, cerebrovascular disease may account for a higher percentage of status epilepticus with a potentially differing response. Our results are limited due to the small sample size, the lack of randomization and inability to standardize concomitant AEDs. Larger, prospective trials are needed to evaluate the efficacy of IV LCM as an early use adjunct or initial treatment in patients with refractory SE.

Authors disclosures

Dr. Lilit Mnatsakanyan reports no disclosure. Dr. Jeffrey M. Chung reports no disclosure. Dr. Evgeny I. Tsimerinov reports no disclosure. Dr. Dawn S. Eliashiv is a consultant for UCB, Lundbeck, Glaxo-Smith Kline and Pfizer.

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